REMARKS

Drs. Harris and Helms are sincerely thanked for their time and help in the interview of Feb. 15, 2007. During that discussion, a Power Point presentation, based in essence on information already of record, was given by Dr. Zardi (a co-founder of Philogen, the assignee of this application). As stated in the Interview Summary, it was agreed by the examiner that this presentation was effective to overcome all the rejections made in the Office Action of Dec. 29, 2006, except for those based on JP(A) H4-169195. In this regard, as further agreed, a copy of the slide presentation is being filed herewith as a summary of the content of the interview.

Insofar as the remaining rejections are concerned, it is the understanding of the undersigned that these also would be withdrawn after the filing of certain further evidence. This relates to submission of literature references with respect to the ELISA results shown in the figure on page 4 of the second Sekiguchi Declaration, dated Sept. 15, 2006. These involve binding studies for the antibody, OAL-TFN-01, an IgM antibody from JP(A)-169195. With respect to the tail of the curve for TFN-01 in the mentioned figure, it was requested that documents be presented confirming the known "stickiness," i.e., non-specific binding, of IgM antibodies in general. Such documents are enclosed.

In Korver et al (p. 242):

> IgM MAbs are known to be larger and more "sticky" than MAbs of the IgG1 subclass (18). In water these MAbs bind nonspecifically to algal and mineral particles, resulting in substantial background fluorescence and false-positive results (24). MAbs of the IgG1 subclass are usually higher affinity and less sticky, thus reducing nonspecific binding and cross-reactivity with other organisms (18).

In Epstein (p. 56):

> A continuing controversy surrounds the inconsistency of test kits for detection of IgM antibodies to HIV. Most test kit manufacturers have avoided the use of IgM-specific conjugates in the indirect ELISA design because of the familiar problem of false positive reactions with specifically "sticky" IgM antibodies.

In Weir et al (p. 745):

> In primary antibody responses, antibodies are generally of the IgM class. Unfortunately, the assay of IgM antibodies may be complicated by the binding of IgM molecules to the test antigen in a non-specific way (Fortier et al., 1982; Torfason and Diderholm, 1982; Boniolo et al., 1983).
>
> In the present study, we encountered such problems when measuring IgM antibodies against KLH. Attempts were made to study the nature of the IgM binding found in pre-immune sera. Several modifications were introduced in the ELISA to minimize these non-specific effects.

In view of these submissions alone, it is believed that this application is now in condition for allowance. However, further relevant information can be seen in Nozawa et al., where Fig. 5B shows what an ELISA assay curve looks like when an IgM antibody (HMMC-1; page 7076, bott. right col.) specifically inhibits binding. Moreover, with respect to the binding experiment of record concerning TFN-01, the lack of its specificity to EDB is also indicated by the following facts.

IgG's (L19) and IgM's (TFN-OAL-01) have different molecular weights (IgG's = ~150,000 Da; IgM's = ~900,000 Da). The experiment of record was run using a molar excess of ED-B (about 9,700 Da). In view of the different molecular weights of IgM's and IgG's, the molar excess of ED-B for TFN-01 was more than 5-fold higher than that for L19. At the concentration used of 100 μg/ml, the molar excess of ED-B vs TFN-01 was close to 5,000 : 1. This is an extremely high molar excess which should be more than sufficient to inhibit the binding of a specific antibody in any biological assay. Despite this huge molar excess, ED-B did not inhibit the binding of TFN-01 to FN. In contrast, L19's binding to FN was completely inhibited with a 10-fold lower ED-B excess (100% inhibition with less than 50μg/ml ED-B). Finally, extrapolation of the sigmoid curve of TFN-01 shows the signal is not pointing towards 0. This indicates that ED-B will not inhibit the binding of TFN-01 to FN even using a higher molar excess. This is a typical indication of non-specific binding.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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